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(54) Title: BACTERICIDAL COMPOSITION

(57) Abstract

There is provided the use of a chelant selected from the succinic acid, glutaric acid, phosphonic acid classes or any salts thereof and mixture thereof as a bactericidal compound. Also provided herein are bactericidal compositions containing said chelant with or without conventional bactericidal agents. Further provided herein is a method for reducing the growth of a bacteria strain, which comprises the step of exposing said bacteria strain to a bactericidal composition of the invention.

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Bactericidal composition

Field of the invention

The present invention relates to the use of a chelant as a a bactericidal compound as well as a bactericidal composition containing a chelant, suitable for use in deodorants, soaps, oral health care, dermatological preparations and also in food as a food preservative. More particularly, it relates to a bactericidal composition comprising a chelant as a bactericidal agent or as a co-bactericidal agent.

Background of the invention

Bacteria may be found in the food or clinic environment. Bacteria strains are divided into two types: gram negative and gram positive. Gram negative bacteria types include bacteria such as Salmonella typhimurium, Bacterioides gingivalis, Actinobacillus actinomycetescomitans, Klebsiella pneumoniae, Escherichia coli and Pseudomonas aeruginosa while gram positive bacteria include bacteria such as Staphilococcus aureus, Streptococcus mutans, Listeria monocytogenes, Streptococcus agalactiae and Coryneform bacteria.

The presence of such bacteria on food or dermatological or oral substrates results in contamination and spoilage. This problem is magnified for gram negative bacteria, especially Pseudomonas aeruginosa as this microoganism is distributed widely and also spreads rapidly since almost any condition is suitable for its growth.

To retard and/or prevent such growth, it is known in the art to use bactericides of the bacterial or chemical type. However, a problem encountered with such bactericides is that they are expensive and/or sometimes are not fully active. Not to be bound by theory, it is believed that the cations present on the cell wall of the bacteria prevent the

bactericidal action. The Applicant has found that the problems of bacteria growth and reduced bactericidal activity are particularly troublesome with bactericidal agents of the chlorophenol and/or quaternary ammonium type.

The formulator thus faces the challenge of formulating a product which maximises the bactericidal activity, minimises the contamination and is also inexpensive.

WO 89/1239 discloses the use of lanthionine containing bacteriocin and a chelating agent for inhibiting Gram negative bacteria growth. More particularly disclosed are lanthionine containing bacteriocins with ethylene diamine tetraacetic acid (EDTA) for inhibiting Pseudomonas aeruginosa growth.

EP 0,639,636 discloses the use of a cationic germicide with a chelating agent and a surfactant. More particularly disclosed are cationic germicides with EDTA and a surfactant for inhibiting gram negative bacteria growth such as Escherichia coli and Pseudomonas aeruginosa.

The Applicant has now surprisingly found that the use of specific chelants of the succinic, glutaric or phosphonic class ameliorate these problems.

It is therefore an object of the invention to provide the use of a compound having a bactericidal activity.

It is another object of the invention to provide bactericidal compositions containing a chelant.

It is a further object of the invention to provide bactericidal compositions containing a chelant together with a conventional bactericidal compound, wherein the combination of said chelant with the conventional bactericidal compound produce a synergistic bactericidal action.

Summary of the invention

The present invention relates to the use of a chelant selected from the succinic acid, glutaric acid, phosphonic acid classes or any salts thereof and mixtures thereof as a bactericidal compound.

Also provided herein are bactericidal compositions containing said chelant together with or without a conventional bactericidal agent.

Further provided herein is a method for reducing the bacterial growth, which comprises the step of exposing said bacteria strain with a bactericidal composition according to the invention.

Detailed description of the invention

Chelant

An essential component of the invention is a chelant. When used as a bactericidal compound per se, the chelant will be present in amount of at least 0.05%, preferably at least 0.7% and more preferably at least 1% by weight of the composition. When used as a co-bactericide, said chelant will be present in amount from at least 0.05%, preferably at least 0.5% and more preferably at least 1% by weight of the composition.

Suitable chelants for the purpose of the invention are compounds selected from succinic acid, glutaric acid, phosphonic acid classes or any salts thereof and mixtures thereof.

Non limiting examples of chelants of the succinic acid class include ethylenediamine disuccinic acid (EDDS), 2-hydroxypropylenediamine disuccinic acid (HPDDS) and any salts thereof and mixtures thereof.

A suitable chelant of the glutaric acid class is ethylenediamine diglutaric acid (EDDG) or salt thereof.

Non limiting examples of chelants of the phosphonic acid class include ethylenediaminetetrakis (methylenephosphonic acid), diethylene triamine penta (methylene phosphonic acid), ethylene diamine tri (methylene phosphonic acid), hexamethylene diamine tetra (methylene phosphonic acid), α-hydroxy-2 phenyl ethyl diphosphonic acid, methylene diphosphonic acid, hydroxy 1,1-hexylidene diphosphonic acid, vinylidene 1,1 diphosphonic acid, 1,2 dihydroxyethane 1,1 diphosphonic acid and hydroxy-ethane 1,1 diphosphonic acid and any salts thereof and mixtures thereof.

Preferred from the above phosphonic acid species is hydroxy-ethane 1,1 diphosphonic acid.

More preferably, said chelants are selected from ethylenediamine disuccinic acid, ethylenediamine diglutaric acid, 2-hydroxypropylenediamine disuccinic acid, hydroxy ethane 1,1 diphosphonic acid or any salts thereof and mixtures thereof.
Especially preferred is ethylenediamine-N,N'-disuccinic acid or the alkali metal, alkaline earth metal, ammonium, or substituted ammonium salts thereof, or mixtures thereof. Preferred EDDS compounds are the free acid form and the sodium or magnesium salt or complex thereof. Examples of such preferred sodium salts of EDDS include Na_2EDDS and Na_3EDDS. Examples of such preferred magnesium complexes of EDDS include MgEDDS and Mg_2EDDS.

In an embodiment of the invention is provided a bactericidal composition comprising a chelant, wherein said chelant is as defined herein before.

In another embodiment of the invention, the bactericidal composition of the invention may further comprise one or more conventional bactericidal agents. The combination of said conventional bactericidal agent with said chelant is seen to produce a synergistic action on bacteria strain, particularly on Gram negative bacteria types and more specifically on Pseudomonas aeruginosa.

Furthermore, the said combination allows the use of a reduced amount of conventional bactericides. More specifically, the combination produces a reduction in the minimum inhibitory concentration (MIC) of the conventional bactericide used per se.
By MIC is meant the "Minimum Inhibitory Concentration", e.g the minimum level necessary of such conventional bactericides to inhibit the bacteria growth.
Determination of said MIC is described hereinafter.

Conventional bactericidal agents
Conventional bactericidal agents of use herein, for the purpose of the invention, will be selected from agents having their original MIC (e.g when used without the presence of a chelant of the invention) reduced by

at least 50%, preferably 70% and more preferably at least 90% when in the presence of said chelant.

Most preferred conventional bactericidal agents which may be used for the purpose of the invention are bactericidal agents selected from chlorophenol and quaternary ammonium species and mixtures thereof. Preferred among the chlorophenol species are compounds selected from 2,4,4' trichloro-2'-hydroxydiphenyl ether available under the tradename Irgasan DP 300 from Ciba Geigy, 2,2'-dihydroxy-5,5'-dibromo-diphenyl ether and mixtures thereof.
Preferred among the quaternary ammonium species is cetyl trimethyl ammonium bromide.

More preferably, these conventional bactericides are selected from 2,4,4' trichloro-2'-hydroxydiphenyl ether (Irgasan DP 300), cetyl trimethyl ammonium bromide and mixtures thereof. A most preferred conventional bactericide to be used in combination with a chelant of the invention is 2,4,4' trichloro-2'-hydroxydiphenyl ether (Irgasan DP 300).

Additional compounds may also be added to the composition. Such additional compounds should not be detrimental to the bactericidal composition of the invention.

Non limiting examples of classes of suitable additional compounds which may be of use herein include surfactants, binders and thickeners.

Surfactant

Non limiting examples of surfactants useful herein, typically at levels from 1% to 95%, preferably 1% to 55% by weight, include the conventional C_{11}-C_{18} alkyl benzene sulfonates ("LAS") and primary, branched-chain and random C_{10}-C_{20} alkyl sulfates ("AS"), the C_{10}-C_{18} secondary (2,3) alkyl sulfates of the formula $CH_3(CH_2)_x(CHOSO_3^-M^+)$ CH_3 and $CH_3(CH_2)_y(CHOSO_3^-M^+)CH_2CH_3$ where x and (y + 1) are integers of at least 7, preferably at least 9, and M is a water-solubilizing cation, especially sodium, unsaturated sulfates such as oleyl sulfate, the C_{10}-C_{18} alkyl alkoxy sulfates ("AE_xS"; especially EO 1-7 ethoxy sulfates), C_{10}-C_{18} alkyl alkoxy carboxylates (especially the

EO 1-5 ethoxycarboxylates), the C_{10-18} glycerol ethers, the C_{10}-C_{18} alkyl polyglycosides and their corresponding sulfated polyglycosides, and C_{12}-C_{18} alpha-sulfonated fatty acid esters. If desired, the conventional nonionic and amphoteric surfactants such as the C_{12}-C_{18} alkyl ethoxylates ("AE"), including the so-called narrow peaked alkyl ethoxylates and C_6-C_{12} alkyl phenol alkoxylates (especially ethoxylates and mixed ethoxy/propoxy), C_{12}-C_{18} betaines and sulfobetaines ("sultaines"), C_{10}-C_{18} amine oxides, and the like, can also be included in the overall compositions. The C_{10}-C_{18} N-alkyl polyhydroxy fatty acid amides can also be used. Typical examples include the C_{12}-C_{18} N-methylglucamides. See WO 9,206,154. Other sugar-derived surfactants include the N-alkoxy polyhydroxy fatty acid amides, such as C_{10}-C_{18} N (3-methoxypropyl) glucamide. The N-propyl through N-hexyl C_{12}-C_{18} glucamides can be used for low sudsing. C_{10}-C_{20} conventional soaps may also be used. If high sudsing is desired, the branched-chain C_{10}-C_{16} soaps may be used.

Other suitable surfactants suitable for the purpose of the invention are the anionic alkali metal sarcosinates of formula:

$$R\text{-}CON(R^1)CH_2COOM$$

wherein R is a C_9-C_{17} linear or branched alkyl or alkenyl group, R^1 is a C_1-C_4 alkyl group and M is an alkali metal ion. Preferred examples are the lauroyl, cocoyl (C_{12}-C_{14}), myristyl and oleyl methyl sarcosinates in the form of their sodium salts.

Mixtures of anionic and nonionic surfactants are especially useful. Other conventional useful surfactants are listed in standard texts.

Binders and thickeners such as sodium carboxymethylcellulose, xantham gum, gum arabic may also be included, as well as synthetic polymers such as polyacrylates, copolymers of polyvinylmethylether with maleic anhydride, copolymers of maleic acid with acrylic acid, terpolymers of maleic/acrylic/vinyl alcohol and hydroxy alkyl cellulose ethers.

Flavours such as peppermint and spearmint oils may also be included, as well as preservatives, opacifying agents, colouring agents, pH-adjusting agents and sweetening agents.

Form of the compositions

The compositions of the invention can be formulated in any desirable form such as powders, granulates, pastes, liquids, tablets, capsules, pills, solutions, suspensions, salves and gels.

Liquid compositions

The compositions of the present invention may be formulated as liquid compositions. Such liquid compositions typically comprise from 94% to 35% by weight, preferably from 90% to 40% by weight, most preferably from 80% to 50% by weight of a liquid carrier, e.g., water, preferably a mixture of water and organic solvent.

Gel compositions

The compositions of the present invention may also be in the form of gels. Such compositions are typically formulated with polyalkenyl polyether having a molecular weight of from about 750,000 to about 4,000,000.

Solid compositions

The compositions of the invention may also be in the form of solids, such as powders, tablets, capsules, pills and granules.

In another embodiment of the invention there is provided a method for reducing the growth of a bacteria strain, which comprises the step of exposing said bacteria strain to a bactericidal composition of the invention.
A particularly effective action is seen on gram negative bacteria and more specifically Pseudomonas aeruginosa.

The invention is illustrated in the following non limiting examples.

Method of determination of the bactericidal activity

1-Preparation of the inoculum

Cultures of the test bacterium were prepared with Pseudomonas aeruginosa in nutrient broth and subcultured at 30°C daily for between three and five successive days before they were required. The inocula were prepared by diluting each of the overnight broth cultures 1:100 in 0.1% Peptone Water immediately prior to use.

2-Determination of the Minimum Inhibitory Concentration (MIC) of EDDS

5ml of the solution of 32.4% trisodium EDDS were added to 5ml of double strength nutrient broth and mixed. 5 ml of this mixture were taken and added to 5ml of single strength broth and mixed. Further halving dilutions were prepared in the same manner until a total of ten dilutions of the product had been prepared.

3-Preparation of solutions of antibacterials

Solutions or suspensions of the antibacterials were prepared in sterile distilled water or water/ethanol mixtures immediately before use.

4-Preparation of nutrient broth containing EDDS

Single strength (0.745%) solutions of EDDS in nutrient broth were prepared by adding 2.3ml of 32.4% trisodium EDDS to 97.7ml single strength nutrient broth. Double strength (1.49%) solutions of EDDS in double strength nutrient broth were prepared by adding 4.6ml of 32.4% trisodium EDDS to 95.4ml double strength nutrient broth.

5-Preparation of dilutions of the antibacterials

5ml of the solution or suspension of antibacterial were added to 5ml of double strength nutrient broth and mixed; 5ml of this mixture were taken and added to 5ml of single strength broth and mixed. Further halving dilutions were prepared in the same manner until a total of ten dilutions of the product had been prepared. This operation was repeated but this time all dilutions were prepared in nutrient broth containing EDDS prepared as in point 4.

6-Determination of the MIC of the conventional bactericidal agents

Halving dilutions in nutrient broth of each antibacterial prepared in triplicate as in point 5 were inoculated with 10 microlitres of the inoculum and mixed. The inoculated broths were incubated at 30°C for 3 days and then examined for visual turbidity. The presence of turbidity, noted "+" in the examples, was taken as an indicator of bacterial growth and multiplication.

Example 1

MIC of trisodium salt of EDDS (Concentration in dilution No1=16.2%)

1	2	3	4	5	6	7	8	9	10
-	-	-	-	-	+	+	+	+	+
-	-	-	-	-	+	+	+	+	+
-	-	-	-	-	+	+	+	+	+

MIC = 0.506-1.013%

At levels of at least 0.7%, EDDS is seen to produce an effective bactericidal action against Pseudomonas aeruginosa bacteria.

Example 2

MIC of Cetyl trimethyl ammonium bromide (ex BDH) (Concentration in dilution No1=0.5%)

1	2	3	4	5	6	7	8	9	10
-	-	-	-	+	+	+	+	+	+
-	-	-	-	+	+	+	+	+	+
-	-	-	-	+	+	+	+	+	+

MIC = 0.0313-0.0625%

MIC of Cetyl trimethyl ammonium bromide in broth containing 0.745% EDDS (Concentration in dilution No1=0.5%)

1	2	3	4	5	6	7	8	9	10
-	-	-	-	-	-	-	-	-	+
-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	+

MIC = 0.000977-0.00195%

It can be seen that the combination of EDDS and cetyl trimethyl ammonium bromide produce a synergistic bactericidal action.

Example 3

MIC of 2,4,4' trichloro-2'-hydroxydiphenyl ether (Irgasan DP 300 ex Ciba-Geigy) (Concentration in dilution No1 =0.5%)

1	2	3	4	5	6	7	8	9	10
-	+	+	+	+	+	+	+	+	+
-	+	+	+	+	+	+	+	+	+
-	+	+	+	+	+	+	+	+	+

MIC = > 0.5%-inhibition in dilution No1 due to presence of ethanol

MIC of 2,4,4' trichloro-2'-hydroxydiphenyl ether (Irgasan DP 300) in broth containing 0.745% EDDS (Concentration in dilution No1=0.5%)

1	2	3	4	5	6	7	8	9	10
-	-	-	-	-	-	+	+	+	+
-	-	-	-	-	-	+	+	+	+
-	-	-	-	-	-	-	+	+	+

MIC = 0.00781-0.0156%

It can be seen that the combination of EDDS and 2,4,4' trichloro-2'-hydroxydiphenyl ether (Irgasan DP 300) produce a synergistic bactericidal action.

WHAT IS CLAIMED IS:

1-The use of a chelant selected from the succinic acid, glutaric acid, phosphonic acid classes or any salts thereof and mixtures thereof as a bactericidal compound.

2-The use of a chelant according to Claim 1, wherein said chelant is selected from ethylenediamine disuccinic acid (EDDS), ethylenediamine diglutaric acid (EDDG), 2-hydroxypropylenediamine disuccinic acid (HPDDS), hydroxy ethane 1,1 diphosphonic acid (HEDP) or any salts thereof and mixtures thereof.

3-The use of a chelant according to either one of Claim 1 or 2, wherein said chelant is ethylenediamine disuccinic acid (EDDS) or salt thereof.

4-A bactericidal composition, wherein said composition comprises a chelant selected from the succinic acid, glutaric acid, phosphonic acid classes or any salts thereof and mixtures thereof.

5-A bactericidal composition according to Claim 4, wherein said chelant is selected from ethylenediamine disuccinic acid (EDDS), ethylenediamine diglutaric acid (EDDG), 2-hydroxypropylenediamine disuccinic acid (HPDDS), hydroxy ethane 1,1 diphosphonic acid (HEDP) or any salts thereof and mixtures thereof.

6-A bactericidal composition according to either one of Claim 4 or 5, wherein said chelant is ethylenediamine disuccinic acid (EDDS) or salt thereof.

7-A bactericidal composition according to any one of Claim 4-6, wherein said chelant is present in amount of at least 0.05%, preferably 0.7% by weight.

8-A bactericidal composition according to any one of Claims 4-6, wherein said composition further comprises a conventional bactericidal agent.

9-A composition according to Claim 8, wherein said chelant is present in amount of at least 0.05%, preferably at least 0.5% by weight.

10-A composition according to either one of Claim 8 or 9, wherein said conventional bactericide is selected from agents having their original Minimum Inhibitory Concentration (MIC) reduced by at least 50%, preferably 70% and more preferably at least 90% when in the presence of said chelant.

11-A composition according to anyone of Claims 8-10, wherein said conventional bactericide is selected from chlorophenol and quaternary ammonium species and mixtures thereof.

12-A composition according to Claim 11, wherein said conventional bactericide is selected from 2,4,4' trichloro-2'-hydroxydiphenyl ether (Irgasan DP 300), cetyl trimethyl ammonium bromide and mixtures thereof, preferably 2,4,4' trichloro-2'-hydroxydiphenyl ether (Irgasan DP 300).

13-A method for reducing the growth of a bacteria strain, which comprises the step of exposing said bacteria strain to a bactericidal composition as claimed in any one of Claims 4-12.

14-A method according to Claim 11, wherein said bacteria strain is of the gram negative type and preferably is Pseudomonas aeruginosa.

INTERNATIONAL SEARCH REPORT

Intc. ational application No.
PCT/US96/09860

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 7/16

US CL :514/358; 424/49

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/358; 424/49

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN: CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,541,944 (SANDERSON) 17 September 1985, see entire reference.	3-6
Y	US, A, 4,719,050 (BLUM et al) 12 January 1988, see entire reference.	3-6
Y	US, A, 5,407,949 (WACHMAN et al) 18 April 1995, see entire reference.	3-6
Y, P	US, A, 5,460,802 (ASAMI et al) 24 October 1995, see entire reference.	3-6
Y, P	US, A, 5,462,692 (ROESLER et al) 31 October 1995, see entire reference.	3-6

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
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Date of the actual completion of the international search 06 SEPTEMBER 1996	Date of mailing of the international search report 02 OCT 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Keith MacMillan Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

Inte. ..tional application No.
PCT/US96/09860

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-3
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 1-3 are drawn to "use of" [a chelant...]. "Use of" claims are non-statutory since they are not among the recognized statutory classes of invention.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [X] Claims Nos.: 7,8,10,11,13 and 14
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.